IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

In re Entresto (Sacubitril/Valsartan) Patent Litigation	C.A. No. 20-2930-RGA [redacted]
NOVARTIS PHARMACEUTICALS CORPORATION, Plaintiff, v. HETERO USA INC., HETERO LABS LIMITED, HETERO LABS LIMITED UNIT III, MSN PHARMACEUTICALS INC., MSN LABORATORIES PRIVATE LIMITED, MSN LIFE SCIENCES PRIVATE LIMITED, Defendants.	PUBLIC VERSION FILED: August 20, 2024 C.A. No. 19-2053-RGA [redacted]

OPENING BRIEF IN SUPPORT OF NOVARTIS'S
MOTION FOR A RULE 62(d) INJUNCTION PENDING APPEAL AND
TEMPORARY RESTRAINING ORDER PENDING RESOLUTION OF THIS MOTION

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I. INTRODUCTION

MSN's accused sacubitril/valsartan ANDA product indisputably infringes Novartis's U.S. Patent No. 8,101,659 ("the '659 patent"), which covers the sacubitril/valsartan drug combination. FDA approved MSN's accused ANDA product on July 24, 2024, making MSN's potential at-risk launch of that product imminent. To prevent an at-risk launch during the currently pending Federal Circuit appeal of the Court's July 7, 2023 decision invalidating the '659 patent for lack of written description, Novartis respectfully moves (i) under Fed. R. Civ. P. 62(d) for an injunction pending resolution of the appeal, and (ii) under Fed. R. Civ. P. 65(b) for a temporary restraining order pending resolution of this motion. Such relief will avoid irreparable harm to Novartis and to the public caused by an at-risk launch, and will allow meaningful review of the Court's decision by the Federal Circuit. If the Court denies Novartis's motion, Novartis then moves for a stay of any at-risk launch for such time as is necessary (*e.g.*, four business days) for Novartis to seek injunctive relief in the Federal Circuit.

II. BACKGROUND

The above-captioned litigation is one of several necessitated by the efforts of MSN and other generic drugmakers to seek FDA approval for generic versions of Novartis's sacubitril/valsartan drug product Entresto® before the expiration and end of any statutory exclusivity of Novartis's patents, including the '659 patent. Novartis's Entresto® (sacubitril/valsartan) is a life-saving, first-in-class heart failure drug whose clinical superiority over previous gold-standard heart failure treatments has been demonstrated repeatedly in clinical trials. Entresto® is currently Novartis's top-selling drug, having generated net sales of $3.067 billion in 2023 in the United States alone. Novartis depends upon those sales to invest in research and development for other critical pipeline drug products, to sustain its efforts to educate

physicians and patients about Entresto®, and to ensure that the significant percentage of patients having heart failure, but who have not yet been diagnosed with or treated for heart failure, learn of the clinical superiority of the sacubitril/valsartan drug combination. An at-risk launch by MSN of its ANDA products will not only cause immediate and irreparable harm to Novartis but will also harm the public by forcing Novartis prematurely to reduce its physician and patient education efforts, thereby causing a significant number of patients to forgo life-saving treatment using Entresto® or generic sacubitril/valsartan drug products.

Beginning in October 2019, Novartis sued MSN and the other generic drugmakers for infringement of the '659 patent, which claims pharmaceutical compositions such as Entresto® that comprise a combination of the drug compounds sacubitril and valsartan. Novartis has since negotiated settlements or stays with most of those generic drugmakers, leaving MSN and Noratech as the remaining Defendants likely to launch their sacubitril/valsartan ANDA products at risk. MSN has stipulated to infringement of the '659 patent (20-md-2930, D.I. 930 at 1).

The validity of the '659 patent was tried to the Court on September 12–14, 2022. In the resulting July 7, 2023 decision, the Court rejected most of the Defendants' invalidity challenges to the '659 patent, including obviousness, enablement, and indefiniteness. 20-md-2930, D.I. 1099 at 1-42, 45-46. Nevertheless, the Court held the '659 patent invalid for lack of written description, concluding that the inventors—as of the January 17, 2002 priority date of the '659 patent—were not in possession of a non-covalently bound complex of sacubitril and valsartan, and thus the '659 patent "axiomatically" could not satisfy the written description requirement. 20-md-2930, D.I. 1099 at 44. Novartis respectfully submits that the Federal Circuit is likely to conclude the Court erred in arriving at that conclusion, as discussed further below. After entry of final judgment on July 21, 2023 (20-md-2930, D.I. 1120), Novartis timely noticed its appeal of the Court's July 7,

2023 decision on July 24, 2023. 20-md-2930, D.I. 1121. That appeal is fully briefed and currently awaiting oral argument.[1]

The litigation stay pursuant to 21 U.S.C. § 355(j)(5)(B)(iii) enjoining FDA approval of Defendants' sacubitril/valsartan ANDAs expired on July 7, 2023. On July 24, 2024, FDA approved MSN's accused ANDA product, making the at-risk launch of that product imminent and the instant motion ripe for resolution.[2] Such an at-risk launch will trigger the at-risk launch of other generic drugmakers due to how the settlement agreements are structured—resulting in a "jailbreak" scenario and amplifying the irreparable harm to Novartis and the public.[3] MSN moreover is unlikely to be able to compensate Novartis for the massive irreparable harm caused by its at-risk launch. Accordingly, Novartis respectfully requests that the Court grant this motion to enjoin the at-risk launch of MSN's ANDA products pending appeal and ensure the Federal Circuit can meaningfully review this Court's judgment.

III. ARGUMENT

Fed. R. Civ. P. 62(d) provides that, "[w]hile an appeal is pending from [a] … final judgment … the court may … grant an injunction on terms for bond or other terms that secure the opposing party's rights." In deciding to grant a Rule 62(d) injunction pending appeal, a court must consider (1) a "movant's chances for success on appeal" and "weigh[] the equities as they affect the parties

[1] On July 30, 2024, the appeal was temporarily stayed by the Federal Circuit while Novartis and defendants Hetero USA Inc., Hetero Labs Limited, and Hetero Labs Limited Unit III sought vacatur of an order and judgment; however, Novartis expects the stay to be lifted shortly.

[2] Novartis did not present the instant request to the Court earlier because MSN did not previously have FDA approval, and because there was a notice stipulation in place (which remains in effect until August 12, 2024), requiring MSN to provide notice to Novartis of any intent to launch at-risk (20-md-2930, D.I. 1092).

[3] Although the terms of Novartis's settlement agreements with generic drugmakers in this matter are confidential, Novartis notes that settlements in Hatch-Waxman suits involving multiple generic drugmakers typically are structured to permit one generic drugmaker to launch following launch by another generic drugmaker.

and the public," including (2) the movant's showing of irreparable harm absent an injunction, (3) any substantial injury to the other parties from an injunction, *i.e.*, the balance of hardships, and (4) the effect on the public interest. *Standard Havens Prods. v. Gencor Indus.*, 897 F.2d 511, 512-13 (Fed. Cir. 1990) (collecting and summarizing cases). The same four-factor analysis applies to a request for a temporary restraining order pursuant to Fed. R. Civ. P. 65(b). *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, No. 09-MD-2118, 2011 WL 1980610, at *1 (D. Del. May 20, 2011).

Courts commonly have issued injunctions pending appeal to prevent the at-risk launch of generic drugs. *See, e.g., Galderma Laboratories L.P. v. Teva Pharms. USA, Inc.*, No. 17-1783-RGA, D.I. 299 (D. Del. Nov. 5, 2019) (Exhibit 19, filed concurrently herewith); *Astrazeneca LP v. Breath Ltd.*, No. 2013-1312, 2013 WL 9853383, at *1 (Fed. Cir. May 24, 2013); *In re Cyclobenzaprine*, 2011 WL 1980610, at *1; *Par Pharm., Inc. v. TWI Pharm., Inc.*, No. 11-2466, 2014 WL 3956024, at *4, *6 (D. Md. Aug. 12, 2014); *Eli Lilly & Co. v. Actavis Elizabeth LLC*, No. 07-3770, D.I. 674 (D.N.J. Aug. 18, 2010) (Exhibit 18, filed concurrently herewith).

Here, all four factors weigh in favor of granting an injunction pending appeal.

a. Novartis Is Likely to Succeed on the Merits of Its Appeal

Patent challengers bear a heavy burden to prove a patent's written description inadequate by "clear and convincing evidence." *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1308 (Fed. Cir. 2015). On appeal from a bench trial, "the district court's interpretation of precedent regarding the written description requirement is reviewed without deference." *Alcon Research Ltd. v. Barr Labs., Inc.*, 745 F.3d 1180, 1190 (Fed. Cir. 2014). Novartis respectfully submits that the Federal Circuit will reverse this Court's judgment holding the '659 patent invalid for lack of written description because this Court misinterpreted precedent and overlooked undisputed facts.

Moreover, "[w]hen harm to applicant is great enough," the need for the movant to show it is "'likely to succeed on the merits'" may be lower. *Standard Havens Prods.*, 897 F.2d at 513. Instead, the movant may show merely "a substantial case on the merits provided that the harm factors militate in its favor." *Eli Lilly and Co. v. Actavis Elizabeth LLC*, No. 2010-1500, 2010 WL 3374123, at *1 (Fed. Cir. Aug. 26, 2010). As explained below, Novartis will suffer massive irreparable harm from an at-risk launch. Thus, granting Novartis the temporary injunctive relief it seeks only requires that the Court conclude that Novartis has shown "a substantial case" on the merits—not a complete showing that the Court's written description ruling is likely to be reversed.

The '659 patent satisfies the written description requirement because there is no dispute the patent identifies, in structural terms, the claimed combination of sacubitril and valsartan. 20-md-2930, D.I. 931 (Novartis's Proposed Findings of Fact) ¶¶ 175, 213-214. The patent's use in the claims themselves and throughout the specification of the exact chemical names and chemical formulas for sacubitril and valsartan provides a precise definition of the claimed combination that allows a person of ordinary skill in the art ("POSA") to recognize that Novartis was in possession of the invention as of January 17, 2002, the '659 patent's priority date. 20-md-2930, D.I. 931 ¶¶ 212, 218; *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350 (Fed. Cir. 2010) (en banc); *Pfizer Inc. v. Teva Pharm. USA, Inc.*, 555 F. App'x 961, 968 (Fed. Cir. 2014). Given these facts, the Court was correct to direct "both sides" at the end of the trial not to "spend a whole lot of time on … the written description [issue]. It seems to me that the Defendants' best two arguments, ***the only ones that have any plausible chance***, are the obviousness and the enablement [arguments]." 20-md-2930, D.I. 883 (September 13, 2022 Trial Tr.) at 505:10–17 (emphasis added).

Federal Circuit precedent precludes holding the '659 patent invalid for lack of written description based on the later discovery of a sacubitril-valsartan complex. Among other things,

under *Ariad*'s common-structural-features test, claims are adequately described if a POSA can "distinguish" the claimed composition from other material based on structural differences. 598 F.3d at 1350. That requirement is met here because a POSA can readily distinguish that the claimed composition is one that includes the precisely defined drug compounds sacubitril and valsartan (including a composition in the form of a sacubitril-valsartan complex like Entresto®'s active ingredient LCZ696). 20-md-2930, D.I. 931 ¶ 219. Such compositions are readily distinguishable structurally from others that omit one or both of those two drug compounds. *Id.* And Novartis's expert Dr. Klibanov gave unrebutted testimony that every composition falling within claim 1 "contain[s] in common the elements of valsartan and the elements of sacubitril." 20-md-2930, D.I. 883 at 423:14-20.

The Federal Circuit has held similar common structural features adequate to satisfy the written description requirement. *See GlaxoSmithKline LLC v. Banner Pharmacaps, Inc.*, 744 F.3d 725, 727, 730-32 (Fed. Cir. 2014). Indeed, there is nothing in the law that requires a patent like the '659 patent to describe every possible permutation of compositions that could infringe. The '659 patent describes the invention as the combination of sacubitril and valsartan and how that combination is useful to treat heart failure, which is enough here to meet the written description requirement. That the patent does not describe a particular complex of sacubitril and valsartan, invented after the patent was filed yet covered by the patent claims, cannot and should not invalidate the patent on written description grounds. At bottom, the complex infringes the patent but does not invalidate it.

Novartis is unaware of any decision holding that a patent claiming and describing the combination of two specific compounds by their chemical names and/or formulas—like the '659 patent—failed to satisfy the "common structural features" test. Instead, this Court relied on

decisions involving a distinct written description problem not present here—the adequacy of a patent's description for claims reciting a broad genus defined in functional terms. *E.g.*, *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1250 (Fed. Cir. 2004); *AbbVie Deutsch/and GmbH & Co., KG v. Janssen Biotech, Inc*., 759 F.3d 1285, 1301 (Fed. Cir. 2014); *see also Regents of the University of Minnesota v. Gilead Sciences, Inc*., 61 F.4th 1350, 1356 (Fed. Cir. 2023) (addressing different issue about whether "broad outlines" in patent provided "blaze marks" to narrower claims); 20-md-2930, D.I. 1099 at 43–45. Properly interpreted, none of those decisions support the conclusion that the '659 patent lacks adequate description, particularly because the Federal Circuit has consistently warned that "whether a patent complies with the written description requirement will necessarily vary depending on the context." *Ariad*, 598 F.3d at 1351.

Accordingly, Novartis respectfully submits that it will succeed on appeal in overturning the only ground on which this Court held the claims invalid, thus reviving its claims.

b. Novartis Will Suffer Irreparable Harm from an At-Risk Launch

Although Novartis believes that it is likely to succeed on the merits of its appeal on the '659 patent, an at-risk launch of MSN's generic ANDA products will cause immediate and irreparable harm to Novartis, even if those products later are withdrawn from the market following an outcome favorable to Novartis on appeal. "When harm to applicant is great enough, a court will not require a strong showing that applicant is likely to succeed on the merits." *Standard Havens Prods.*, 897 F.2d at 513 (cleaned up). Moreover, there is a clear factual nexus between the sacubitril-valsartan combination claimed by the '659 patent and the demand for MSN's infringing sacubitril/valsartan ANDA products, because—as with Entresto®—it is the claimed combination of sacubitril and valsartan that is responsible for the therapeutic efficacy of those products in the treatment of heart failure. *See* 20-md-2930, D.I. 930 at 21 (undisputed that there is a nexus

between the claims of the '659 patent and Entresto®'s therapeutic efficacy). *See also Teva Pharms. Int'l GmbH v. Eli Lilly & Co.*, 8 F.4th 1349, 1361 (Fed. Cir. 2021) (with respect to objective indicia of non-obviousness, "a new and unobvious pharmaceutical compound would surely have a nexus to the marketed finished product sold to consumers").

The relevant facts concerning irreparable harm are set forth in the expert declaration of Christopher Vellturo, filed concurrently herewith. The primary forms of irreparable harm that Novartis and the public will suffer from an at-risk launch are summarized below.

Loss of market momentum, lost sales, lost market share, lost formulary position and price erosion: Entresto® is currently Novartis's top-selling drug, having generated $3.067 billion in net U.S. sales in 2023 alone. Vellturo Decl. ¶ 10. Those blockbuster sales have been driven by increasing Entresto® prescriptions, in view of Entresto®'s clear clinical superiority over other heart failure treatments and recently updated clinical guidelines that more strongly recommend Entresto®. *Id.* ¶¶ 30, 61. Since 2020, Entresto®'s annual sales have continually beat Novartis's most optimistic internal forecasts in view of the large and growing pool of undiagnosed and/or untreated heart failure patients who may benefit from, but have not yet been treated with, Entresto®. *Id.* ¶¶ 31–32, 59–62.

An at-risk launch by MSN of its sacubitril/valsartan ANDA products (*i.e.*, "generic entry") is also likely to trigger at-risk launches by other generic drugmakers, thereby destroying Entresto®'s market momentum and causing Novartis to suffer immediate and irreparable harm in the form of lost sales, lost market share, loss of formulary position, and price erosion. *Id.* ¶¶ 50–57 (describing the effects of generic entry on sales volume, formulary position, and price); 40, 69–74 (describing the effects of generic entry on market momentum and market share). Given the sheer size of Novartis's Entresto® sales, those losses will be massive, and the monetary damages

resulting therefrom likely will be beyond MSN's ability to pay. *Id.* ¶¶ 63–67. *See Celsis in Vitro, Inc. v. CellzDirect, Inc.*, 664 F.3d 922, 930-31 (Fed. Cir. 2012) (competition from alleged infringer against patentee's flagship product, when that product was in its "growth phase" and was about to achieve its "highest revenues," constituted evidence of irreparable harm). In that way, those losses will be irreparable.

Those losses, to some extent, will also be permanent. Even if MSN's and others' generic products are later withdrawn from the market, Novartis is unlikely to be able to raise prices to pre-generic entry levels due to resistance by large third-party payers (*i.e.*, Medicare, private insurers, and managed care organizations) to any future price increases, and the damage to Novartis's goodwill that would result from such price increases. Vellturo Decl. ¶ 69. Courts have found price erosion and damage to the goodwill of a branded drug manufacturer to constitute forms of irreparable harm. *See, e.g.*, *Novartis Pharms. Corp. v. Accord Healthcare Inc.*, No. 18-1043, D.I. 583 at 7 (D. Del. June 24, 2019) (memorandum order granting preliminary injunction and finding irreparable harm where generic entry would lead to "massive and immediate price erosion," where "Novartis will not be able to raise the price back to where it is now, or to where it would have been at that post-trial date in the absence of defendants' at-risk infringement," and where Novartis would risk harm to its goodwill if it attempted to do so) (Exhibit 20, filed concurrently herewith); *Par Pharm., Inc.*, 2014 WL 3956024, at *4 (finding irreparable harm where "there is evidence that were TWi to enter the market only to be required to exit again, the price erosion and revenue losses Megace ES would suffer would be impossible to reverse completely"). *See also Polymer Techs., Inc. v. Bridwell*, 103 F.3d 970, 975–76 (Fed. Cir. 1996) ("Years after infringement has begun, it may be impossible to restore a patentee's … exclusive position by an award of damages and a permanent injunction … Requiring purchasers to pay higher prices after years of paying lower

prices to infringers is not a reliable business option."); *Celsis in Vitro, Inc.*, 664 F.3d at 930 (noting that price erosion and loss of goodwill are "valid grounds for finding irreparable harm"). And, as discussed below in connection with the public interest, the reduction of Novartis's physician and patient education efforts due to generic entry will cause a significant number of heart failure patients to forgo treatment with Entresto® or generic sacubitril/valsartan products, thereby permanently ceding market share to alternate treatments.

The full extent of those losses will be difficult—if not impossible—to calculate. Although actual Entresto® and generic sacubitril/valsartan sales during the period of generic competition can be determined, the complicated and changing dynamics of the heart failure drug market (including competition from new categories of heart failure drugs), uncertainty over how payers will respond to the entry and subsequent withdrawal of generic products, and the importance of physician and patient education to Entresto®'s continued market momentum, make it hard to predict what Entresto® sales would have been ***but for*** generic entry, and thus the true extent of the harm that Novartis will experience following generic entry. Vellturo Decl. ¶¶ 58–62. This makes an injunction now all the more important.

Impaired promotion of other cardiovascular drugs: Novartis's cardiovascular salesforce promotes not only Entresto®, but other cardiovascular drugs. *Id.* ¶ 75. An at-risk launch will necessarily impair that salesforce and the resources available to them, which not only will contribute to the destruction of Entresto®'s market momentum but also will impair Novartis's promotion of new and forthcoming cardiovascular drugs, including the recently launched cholesterol-lowing drug Leqvio®. *Id.* ¶¶ 75–77. Such disruptions at the early stage of the life cycles of those new and forthcoming drugs will imperil their future benefit to patients, as well as

profitability. *Id.* The full extent of those effects will be difficult, if not impossible, to calculate. *Id.* ¶ 77.

b. The Balance of Hardships and the Public Interest Favor the Grant of a Preliminary Injunction

An at-risk launch by one or more Defendants of their sacubitril/valsartan ANDA products not only will cause irreparable harm to Novartis but will also upset the balance of hardships and harm the public, including the health of heart failure patients who may benefit from treatment with a sacubitril/valsartan product.

Balance of hardships: The potential injury that MSN would face from a delayed launch due to a Rule 62(d) injunction pending appeal is significantly outweighed by the harm Novartis would likely incur from an at-risk launch. Due to the lower price of the MSN's generic ANDA products, its profits will be significantly less than the losses Novartis will sustain. Vellturo Decl. ¶¶ 78–79. Put simply, Novartis stands to lose far more than MSN will gain from an at-risk launch. And for that reason, MSN is unlikely to be able to pay Novartis for those losses.

Moreover, the requested Rule 62(d) injunction would need to last only as long as it takes for the Federal Circuit to resolve Novartis's appeal, and any potential injury to MSN can be addressed by a bond. *See* Fed. R. Civ. P. 62(d) ("[T]he court may … grant an injunction on terms for bond or other terms that secure the opposing party's rights."). The balance of hardships thus favors the grant of injunctive relief.

Public harm due to reduction of physician and patient education efforts and patient support programs: Last but not least, generic entry will cause real harm to the public. Heart failure patients tend to be under-diagnosed, and many heart failure patients are not treated even when they have a diagnosis. Vellturo Decl. ¶¶ 32, 71, 81. To address those treatment gaps, Novartis devotes considerable efforts to physician and patient education, which are sustained by

Entresto®'s sales. *Id.* ¶¶ 32, 71–73, 81. An imminent at-risk launch will cause Novartis to reduce such efforts. *Id.* And because generic drugmakers are unlikely to undertake any physician or patient education efforts of their own, a significant number of heart failure patients who would have been reached by those efforts, and who would have benefitted from treatment with Entresto® or a generic sacubitril/valsartan product, likely will forego such treatment following generic entry. *Id*. ¶¶ 73, 81.

Additionally, generic entry will force Novartis to reduce its patient support programs for Entresto®, which include a call center, a co-pay assistance program, and a 12-month patient lifestyle program with live support specialists to improve patient adherence. *Id.* ¶¶ 70-71. Reduction of those patient support programs will negatively affect patients who currently are being treated with Entresto® and may even cause such patients to stop their treatment prematurely. *Id.* ¶¶ 73, 81. The resulting harm to those patients and to the public in those circumstances is apparent.

IV. CONCLUSION

For the reasons above, Novartis's motion for a Rule 62(d) injunction pending appeal and a temporary restraining order pending resolution of this motion should be granted.

Date: August 2, 2024

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CERTIFICATE OF SERVICE

The undersigned counsel hereby certifies that true and correct copies of the foregoing document were caused to be served on August 2, 2024 on the following counsel in the manner indicated below.

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